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## Internet Based Training of Coronary Artery Patients: The Heart Cycle Trial

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## ABSTRACT

### Background:

Low adherence to cardiac rehabilitation (CR) might be improved by remote monitoring systems that can be used to motivate and supervise patients and tailor CR safely and effectively to their needs. The main objective of this study was to evaluate the feasibility of a smartphone guided training system (GEX) and whether it could improve exercise capacity compared to CR delivered by conventional methods for patients with coronary artery disease (CAD).

### Design:

A prospective, randomized, international, multi-center-study comparing CR delivered by conventional means (CG) or by remote monitoring (IG) using a new training steering/feedback tool (GEx System). This consisted of a sensor monitoring breathing rate and the electrocardiogram that transmitted information on training intensity, arrhythmias and adherence to training prescriptions, wirelessly via the internet, to a medical team that provided feedback and adjusted training prescriptions. Exercise capacity was evaluated prior to and six months after intervention.

### Results:

118 patients ( $58 \pm 10$  years, 105 men) with CAD referred for CR were randomized (IG:  $n=55$ , CG:  $n=63$ ). However, 15 patients (27%) in the IG and 18 (29%) in the CG withdrew participation and technical problems prevented a further 21 patients (38%) in the IG from participating. No training related complications occurred. For those who completed the study, peak  $VO_2$  improved more ( $p=0.005$ ) in the IG ( $1.76 \pm 4.1$  ml/min/kg) compared to CG ( $-0.4 \pm 2.7$  ml/min/kg).

## Conclusion:

A newly designed system for home-based CR appears feasible, safe and improves exercise capacity compared to national CR. Technical problems reflected the complexity of applying remote monitoring solutions at an international level.

**Key Words:** Exercise training, cardiac rehabilitation, monitoring

### a. ABBREVIATIONS

BF	Breathing frequency
BP	Blood pressure
CAD	Coronary artery disease
CG	Control group
CPX	Cardiac exercise testing
CR	Cardiac rehabilitation
CTC	Central Training Committee
dO <sub>2</sub> /HR	aerobic workrate
EF	Ejection fraction
GEx	Guided Exercise
HF	Heart failure
HR	Heart rate
HRR	Heart rate reserve
IG	Intervention group
MI	Myocardial infarction
O <sub>2</sub> /HR	oxygen pulse
PC	Personal Computer
QoL	Quality of life
VO <sub>2</sub> peak	Peak oxygen uptake

## **b. INTRODUCTION**

Cardiac rehabilitation (CR) aims at restoring exercise performance [1] in patients after a cardiac event like myocardial infarction (MI) [1], peripheral arterial disease [2,3] or heart failure (HF).[3-7] CR uses multifactorial intervention, including aggressive risk factor modification [8-11,7]. Traditionally, these programs have tried to improve physical health and individual attitude through exercise-only based CR or comprehensive CR (e.g. smoking cessation, dietary counseling as well as exercise).[8] Meta-analyses on exercise based CR showed a significant reduction in cardiac mortality of about 27% compared to patients receiving conventional care.[9],[12] Still, there are relevant national differences in how CR programs are organized.[9] Unfortunately, despite efficacy and cost-effectiveness CR, is pursued by less than one-third of eligible patients.[13] As beneficial effects of CR largely depend on continuation of a lifetime exercise program after a structured CR, patients should be encouraged to continue with an individual exercise program to preserve an improvement in exercise capacity. [8,10,11,13-18]

Reasons for non-participation in CR included unavailability of hospital-based CR, lack of motivation or other reasons e.g. excessive travel distance [19] Quality performance criteria, automated referral systems and options for home-based CR services may increase adherence to therapies in some patients. Besides centre-based CR, home-based CR offers a potentially valuable alternative for many individuals [20-22], and has proved to introduce similar improvements compared to center-based programs across a range of measures [23] at lower [24] or comparable cost.

These findings would support an extension of home-based CR as an attempt to widen access and participation.[25-27] Furthermore, the evolution of the technology has led to the design of mobile-based solutions which could facilitate home based CR and overcome

1 patient safety concerns.[28-32] The GEx system [33-35], designed under those requirements,  
2 introduces a closed-loop disease management system supporting the prescription and  
3 administration of CR. A feasibility study was previously performed to compare signals of this  
4 new system with standard cardiac exercise testing (CPX) during inpatient phase-II-CR that  
5 showed the suitability of the whole system for monitoring of home-based CR [36] with  
6 accurate heart rate (HR) measurements. In this present study improvements obtained due to  
7 long-term home-based CR (CR- phase III) were determined. Guided exercise training  
8 supervised by the GEx system was compared to the standard care in three different  
9 countries (Great Britain, Spain, Germany).

## 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 **c. METHODS**

### 28 29 30 31 **Study design and study objectives, ethical considerations**

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33 In this open, prospective, randomized, parallel group, German, British and Spanish, three-  
34 center, Phase I study, the standard national approach to CR was compared to an approach  
35 adding the new training steering and feed-back GEx System. All patients were recruited  
36 during phase II cardiac rehabilitation in Spain, GB and Germany to compare national  
37 difference in CR. The study was performed after discharge from rehabilitation facilities at  
38 home (phase III rehabilitation) with individual training prescription. Patients were  
39 randomized to an intervention group (IG) and a control group (CG). Overall, treatment was  
40 according to national CR recommendations. Additionally, patients randomized to the IG  
41 were equipped with the GEx System.

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The main objective of this study was to evaluate, whether the GEx System can  
improve physical exercise capacity at 6 months follow up during home based, phase III CR

1 compared to national CR standards. Secondary objectives were to evaluate the effect of the  
2 GEx System on compliance, total exercise time, fear and anxiety, physical fitness, symptoms  
3 and whether home training was safe as well as serum cholesterol, LDL and fastening  
4 glucoses blood pressure (BP) control, QoL and ejection fraction (EF) .  
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10 The Regional Ethical Review Board at the University of Aachen (00017326, EK218/11),  
11 Hospital Clínico San Carlos of Madrid (C.I. 11/232-E) and University of Hull (12/YH/0072)  
12 approved the study. Principles according to the Helsinki declaration (WMA 2008) were  
13 followed. Written informed consent was obtained from all participants prior to inclusion in  
14 the study. Also, the study was registered at *ClinicalTrials.gov* (identifier NCT01761448).  
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## 27 **Inclusion and exclusion criteria**

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29 Inclusion criteria were: presence of CAD after acute MI or elective coronary  
30 intervention,  $EF \geq 30\%$ , willing to exercise, eligible for CR and ability to use computer and  
31 Internet. Respectively, exclusion criteria were:  $EF < 30\%$ , HF with NYHA IV, inability to  
32 exercise, severe valve disease, recent cardiac surgery < 4 weeks, implantable devices (ICD or  
33 CRT-device, pacemaker) or open thorax wound.  
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## 47 **Study phases and data acquisition**

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49 All patients underwent an initial baseline evaluation consisting of a careful history  
50 taking (with activity profile evaluation) and a physical examination. A standard ECG,  
51 laboratory analysis, 2D echocardiography and exercise testing with additional lactate  
52 samples was carried out. All individuals were asked to fill in QoL questionnaires.  
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During the 6-month training phase, patients in the IG performed training under guidance of the GEx system. Individual training performance was closely monitored and exercise prescriptions were continuously reviewed and adjusted as needed. This was done by a dedicated team of sport physicians and exercise scientists, the so-called Central Training Committee (CTC). Patients in the IG were evaluated with respect to usability of the system, knowledge about heart-related health, exercise habits and adaption efforts. In contrast, patients in the CG were asked to report on daily physical activities on a paper dairy.

At 6 month FU, all baseline examinations were repeated in both groups.

### ***Laboratory parameters***

Urea clearance, potassium, sodium, white/red blood cell count, platelet count, total cholesterol, LDL- cholesterol, HDL, Cholesterol, HbA1c, hsCRP, ntBNP were analyzed.

### ***ECG***

A standard electrocardiography was performed using a commercial system at each site.

### ***Echocardiography***

A standard 2D-echocardiography was performed using available systems at the different sites. All standard views (2 and 4-chamber view) were acquired. Left ventricular EF was then calculated according to Simpson's method.



## ***Quality of life***

All patients were instructed to complete questionnaires regarding QoL (EQ5D)[37] and anxiety and depression (HADS)[38].

## ***Cardiopulmonary exercise testing (CPX)***

A cardiopulmonary exercise testing (cycle ergometer) starting at 25 W, with increments of 25 W per 2 minutes (incremental), was performed. Peak oxygen uptake ( $VO_{2\text{peak}}$ ) at peak exercise was defined as the highest oxygen consumption measured during the last 30 s of the symptom-limited exercise test and expressed as ml/kg/min.  $VO_2$  (ml/kg/min),  $VCO_2$  (L/min), and  $VE$  (L/min) were collected throughout the test.  $VE$  and  $VCO_2$  were designated as the y- and x-axis variables, respectively.  $VE/CO_2$  slope was calculated with the slope calculation option of the software package. In Aachen Carefusion Masterscreen CPX, Lab Manager Version 4.67 was used, in Hull Innocor by Innovision and in Spain Ergostik Geratherm were applied. HR was taken through 12 lead ECG. BP was taken using an automated BP machine with integrated microphone (Getemed). During testing, relevant ischemia, arrhythmias, HR and BP were evaluated. For anaerobic threshold v-slope method was used. [39,40]. Also HR reserve (HRR, normal < 20 bpm), oxygen pulse ( $O_2/HR$ , ml/beat) and aerobic workrate  $dO_2/dW$  (normal > 10 ml/min/W) [41,42] were determined.

Lactate concentration was measured at baseline and at every exercise step. Specifically, HR and watt at 2mmol lactate and at 4mmol lactate were obtained.

## Guided Exercise System (GEx)

The GEx system is a closed-loop disease management system facilitating prescription and administration of CR therapies[36] made up of three main components: *Professional System*, *Patient Station* and *Portable Station*.

The *Professional System* is a web-based tool for medical professionals (Figure 2) providing information on the patients' profile with respect to medical history and CR prescription and performance in the past. Furthermore, data from the patients' systems (*Portable Station* and *Patient Station*) including HR, BP, notifications on events during exercise session and ECG tracings are displayed.

The *Patient Station* acts as the gateway between the *Portable Station* and the *Professional System*, as it is able to synchronize exercise plans prescribed by professionals and extract monitored data from the portable station and upload them to the professional system. It is also in charge of providing educational material and motivational feedback generated from actual exercise performances.

The *Portable Station* (Figure 1) is used by the patient during prescribed exercise sessions. It includes a sensor for acquisition of vital signs and a smart-phone for interaction with patients. The smart-phone software contains algorithms that process the vitals collected from the sensor and, based on the individual exercise plan, provide immediate feedback with respect to training intensity (Figure 2).

In order to ensure patients' safety and to avoid hazardous situations, a series of verifications were implemented prior to each CR session (cardiac symptoms (angina pectoris, dyspnea), well-being, blood pressure). Patients received immediate feedback on whether it was safe to exercise or if it was better to reschedule the exercise at a later point in time.

## **Training prescription/ Central Training Committee (CTC)**

The CTC was created to obtain individual training prescription for all patients at all trial sites based on a homogeneous strategy. The information gathered during initial exercise testing was sent to the Institute for Cardiology and Sports Medicine, German Sports University Cologne, Germany for all patients. This held also true for retesting performed during the training phase. At the CTC, individual exercise prescriptions for each patient participating in IG of the study were elaborated and sent back to the study site. Importantly, all changes in medication, especially beta-blockers and calcium channel blockers had to be announced to the training committee.

In case a patient failed to follow the training prescription or was at risk of over-exercising, the CTC had to be notified to assess whether a change in the training prescription was needed.

## **Description of training content**

Patients were instructed to perform training sessions containing endurance but also resistance training. The goal of the endurance training (e.g. cycling, walking) was to make the patient work out in a safe but also effective HR zone. Consequently, patients' HR was supposed to stay in an individual, pre-defined target zone. [43]

Resistance training was a combination of both isometric and isotonic exercises using a rubber band.

### *Intensification strategy*

The intensification strategy followed the FITT [44,45] (frequency, intensity, time and type of activity) principles model. GEx patients indeed followed a training plan consisting on three stages as described in Figure 3.

### **Power calculation, randomization and statistical analysis**

According to previous literature [46,47], it is feasible to expect a 3 ml/min/kg standard deviation of the main variable (VO<sub>2</sub>max). A sample size of 130 analyzable patients (65 per group) would therefore have adequate power (80%) at a 5% level of significance (one-tailed) to show a 1,3 ml/min/kg difference. In order to meet the minimum sample size requirements for the objectives, accounting for possible study attrition (e.g. subject death, withdraw of consent), the study was meant to enroll a total of 150 subjects. More specifically, 25 patients per group were expected for each study site, thus, 50 patients were meant to be included at each site. Overall, 75 patients for each randomization group had to be allocated. All analyses of secondary endpoints were regarded as exploratory. The explorative approach were concomitant the explanation not to adjust for multiple comparisons. The p-values were therefore merely descriptive.

All data were stored in an eCRF using the number of randomized patient as identification.

Randomization stratified by 'gender' and 'centre' was done electronically by the system (eCRF). To evaluate the number of patients that matched with the inclusion and exclusion criteria, a screening list was carried. Due to the kind of intervention, the study had to be performed open-labeled. The un-blinded design seemed to be appropriate to reach

primary objectives. However, physicians/technicians performing and evaluating echocardiography or functional testing were unaware of the study group.

Continuous data was summarized by the median (interquartile range); categorical data by percentages. A two-tailed Student's t test was used for comparison between groups. Linear regression was used to adjust for baseline covariates (age and sex as a minimum). Residuals were checked for normality. Either Fisher's exact test or Chi-squared test were used for categorical variables with nominal scales and the Mann-Whitney U test for categorical variables with ordinal scales. Missing values were not imputed but reported in Tables. All tests were assessed at the 5% statistical significance level. The 'Stata' statistical computer package was used to analyze the data.

## **d. RESULTS**

### **Patients' characteristics**

Starting on 4/2011, 132 patients ( $59 \pm 14$  years, 11 % females) gave consent (33 in Aachen, Germany, 44 in Hull, GB and 55 in Madrid, Spain). Of these, 89 % were randomized and included in the study: 63/53% were assigned to the CG and 55/47% to the IG (table 1). The patients' characteristics are stated in Table 2. Patients were recruited during the phase II rehabilitation. This allowed all patients to enter the study at the same stage, thus, delivering the same information to all patients at the same point in time. Furthermore, the phase II could be used to make patients familiar with the new training tool and provide time for further instructions.

All patients were on standard medication for CAD (table 2). Table 2 shows the baseline exercise characteristics of the patients consented. Furthermore quality of life

characteristics at the beginning of the study are stated in table 2, showing no difference between anxiety, depression and EQ-5D at baseline.

### **Randomization and follow-up**

In the IG, 15 patients (27%) dropped out before starting the guided rehabilitation. Of those actually participating in the program 12(30%) finished all interventions. However, 17(8%) showed poor compliance and 21 patients (53%) stopped during the training phase due to several reasons: lack of time, issues with Internet connectivity, demotivation because of safety algorithms delaying or stopping exercise too often, follow up was already too late, or no training was allowed due to chronic infections or chronic back pain.

In the CG, n=15 patients denied participation in the study and n=3 patients cancelled follow-up investigations.

### **Training sessions and safety algorithm**

In effect, only 43% of the exercise sessions were fully completed, other 37% were interrupted by the safety algorithms, 20% where abandoned because of technical errors (e.g. poor signal quality or poor communication with sensor), and 2% were explicitly stopped by the users.

This may explain why some users got annoyed by the safety measurements. More concretely, of these interruptions, 63% were because of high BP, 26% because of HR values out of range for too long and the remaining 2% because of other reported symptoms.

## **Safety of cardiac rehabilitation**

Adverse events were reported in 6 patients (31%) in the IG and 3 patients (8%) in the CG. However, there was no complication directly associated with CR. More specifically, in the IG 2 patients complained of chest pain based on chest infection after CABG, 2 patients were admitted to hospital with consecutive angiography due to new onset of angina pectoris which was not related to training and 2 patients contacted the study center because of chest pain before training and were sent to hospital for further investigation resulting in CABG because of progression of disease. In the CG, reasons for adverse event were new onset of atrial fibrillation (n=1), new angina at rest (n=1), which resulted in angiography without intervention and pseudo aneurysm of the right femoral arteries after PCI (n=1) with surgery intervention.

## **Outcome of the primary endpoint**

If compared between CG and IG, the use of the GEx system results in a statistically higher improvement in VO<sub>2</sub>peak (Table 3).

In both groups, CR resulted in reduction of HR at rest and at anaerobic threshold, reduction of VE/VCO<sub>2</sub>-slope, increased maximum watts, reduction of lactate levels at 4, 6, 8 and 10 minutes during exercise. However, there was no significant difference with respect to increase in the latter parameters between the two groups.

## **Outcome of the secondary endpoints**

### *Clinical parameters*

BMI in the CG and IG showed no significant reduction. (Table 3).

### *Echocardiography parameters*

Additionally, training in the CG group showed a significant decrease in EF, whereas in the IG group the EF was increased. Also, there was a significant difference between the group regarding change in EF ( $p=0.004$ ) (Table 3).

### *Laboratory parameters*

Training results in both groups in a non-significant reduction of total cholesterol, LDL and fasting glucose, reduction of hsCRP and nT-pro-BNP-levels (Table 7). Statistically, there was no significant difference between the two groups (Table 4)

### *Quality of life*

Comparison of anxiety and depression and EQ-5D showed no significant difference between CG and IG (Table 5).

## **e. DISCUSSION**

The main finding of this study is that home CR was feasible and safe. Furthermore, it seems that adequate use of the GEx system had a substantial effect on exercise capacity compared to standard CR in patients with cardiac disease.

Unexpectedly, some problems were encountered with the safety mechanism implemented in the portable device, which completely prevented patient participation or caused frequent delays leading to patient frustration and de-motivation. There may be



several reasons for it: patients started exercising with too high intensity during the warm-up or the target HR limit was so low during warm-up that it was difficult to keep HR there. Several sessions were cancelled or delayed also because of the safety measures used with BP values. That safety mechanism included research algorithms that had not been extensively tested with CAD patients and therefore were not optimized. An important note for the future is that the target HR zone should be wide enough so that the user is able to keep HR within the target and BP safety thresholds should be better tailored to patient's conditions. These issues would have been readily surmountable had a prototype safety algorithm been clinically tested in advance with a sufficient number of patients or had there been more time to conduct the study.

Although there were technical problems, the system was accepted by users as also confirmed by a specific acceptance questionnaire.

In conclusions, for those patients who were not affected by the security algorithms, quality of the HR signal was good and the patients were able to keep their HR within the prescribed HR zone.

## **f. LIMITATIONS**

Due to some technical problems and the strict behavior in the safety mechanisms, only a limited number of patients were able to reach the final study point. Still, the GEx Study demonstrated a considerable improvement in cardio-pulmonary performance with a remotely supported training program compared to standard CR. Indeed, the magnitude of effect appeared substantially greater than with other exercise training programs that depend on patients attending classes and complying with exercise prescriptions at home,

1 between classes, without remote support. The number of dropouts was disappointing but  
2 does not detract from remotely supported rehabilitation as a proof of concept. Some  
3 technical issues can be fixed, more lax safety algorithm can be implemented and the  
4 methods and implementation of the exercise prescription can certainly be improved. This  
5 trial provides the impetus to scale up the intervention to manage much larger patient  
6 groups, potentially in the context of further randomized controlled trials.  
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## 16 **g. CONCLUSION**

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18 The GEx system for home based CR showed to be feasible and successful as compared  
19 to three different national CR systems (GB, Spain, Germany). It improved exercise capacity,  
20 was associated with reduction of weight, levels of hsCRP and cholesterol-levels. Training  
21 sessions were safely performed. Still, a more mature technological solution is required to  
22 make it an alternative for today's standard CR approach.  
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33 Unfortunately the major loss to follow-up weakens any conclusions that can be  
34 drawn from the study. However, the study could be viewed as an important proof-of-  
35 concept that can be refined for deployment in more substantial clinical trials.  
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## **h. CONFLICT OF INTEREST**

Erik Skobel and Christian Knackstedt have received consultant honoraria from Philips, coordinator of the Project HeartCycle.

## **i. FUNDING**

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## I. TABLES

Table 1: Inclusion of patients

Table 2: Patient characteristics at baseline

Table 3. Exercise characteristics of control group and interventional group at the end of the study period, \*:  $p < 0.05$

Table 4: Blood parameters at the end of the study period, comparison between CG and IG

Table 5: QoL-indices at the end of the study period, comparison between CG and IG

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3 **m. FIGURE ANNOTATIONS**  
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10 Figure 1: Components of the portable station a) ECG-Sensor, b) west c) PDA attached to the  
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12 arm d) PDA for training  
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18 Figure 2: Web based training database  
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21 Web based training data base. A status bar on the bottom of the screen where  
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23 specific information about the logged user is displayed:  
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27 User name, Status message on the actions the user performs in the system,  
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30 Language selection. Patients training data is visible and progress of training process.  
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36 Figure 3: Cardiac exercise program  
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Site	Cons ente d	Study Group	Randomi zed	Started Intervent ion	Dropped Out after Starting	Poor Compli ance	Final Test Done *1
Germany	33	C	18		2		10
		I	14	12	4	1	8
Spain	55	C	25		10		15
		I	17	4	3	1	1
UK	44	C	20		3		17
		I	24	24	14	5	3
Total	132	C	63		18		42
		I	55	40	21		12

Table 1: Inclusion of patients

<sup>1</sup> Includes patients with poor compliance: <50% of expected training sessions

Table 2: Patient characteristics at baseline

Variable	Missing	Control (n=63)	Intervention (n=55)
Age (years)		58(52,67)	60(50,65)
Sex (men)		55(87%)	50(91%)
BMI(Kg/m <sup>2</sup> )		27.7(25.1,30.8)	28.4(25.3,32)
SBP(mmHg)		130(113,140)	129(120,140)
DBP(mmHg)		77(70,83)	80(72,87)
Total cholesterol(mmol/L)	20	139(123,165)	154(136,180)
Glucose(mg/dl)	12	100.9(86,115)	97(88.2,132)
NTproBNP(ng/l)	16	194(83,498)	209(71,721)
Ejection fraction(%)	5	61(57,70)	56(50,65)
ACE-Inhibitors (n,%)	0	32 (50)	33 (58)
ARB (n,%)	0	17 (26)	13 (23)
Aspirin (n,%)	0	55 (85)	52 (92)
Betablockers (n,%)	0	54 (84)	44 (78)
Calciumchannelblockers (n,%)	0	4 (6)	6 (11)
Diuretics (n,%)	0	8 (13)	12 (21)
Nitrates (n,%)	0	10 (16)	21 (37)
Statins (n,%)	0	58 (90)	53 (94)
Spironolactone (n,%)	0	1 (2)	1 (2)
Exercise time(min)	12	8(8,10)	8(8,10)
Maximum Watts(W)	4	125(100,150)	125(100,150)
Resting HR(bpm)	10	71.7 (44,103)	72 (46,107)
VO <sub>2</sub> (ml/min/Kg) AT	10	12.8(11.7,15.9)	13.8(10.9,16.7)
Peak VO <sub>2</sub> (ml/min/Kg)	30	20(17,23)	21.5(17.2,24.8)
O <sub>2</sub> (ml/beat)	5	13.3(11,15.5)	12.6(10.9,15.8)
dO <sub>2</sub> /dW (ml/min/W)	4	10.1(8.9,11.8)	10.3(8.7,11.3)
VEV/CO <sub>2</sub> ratio	13	32.5(28.2,36)	33.5(29.7,42)
HRR (bpm)	4	50(38,63)	47(37,64)
HADS anxiety (Points)	26	20(17,21)	19(18,21)
HADS depression (Points)	26	16(15,17)	16(15,16)
EQ-5D (Points)	10	70(60,85)	80(70,90)

Notes. Data shown are median (25<sup>th</sup>/75<sup>th</sup> centiles) or n(%). BMI=body mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. HR=heart rate.

	M V	End of Study Contr ol Grou p	P (versus Baselin e)	M V	End of study Interventio nal group	P (versus baselin e)	Delta Contr ol group	Delta Interventio nal group	P (delta control vs. delta interventio nal)
N=		42			19		42	19	
Maximum Watts (W)	0	118.4 ± 35	0.78	0	126 ± 47	0.95	4.6 ± 35	11.6 ± 15	0.32
Exercise Time (min)	12	8.1 ±1.9	0.77	1	8.4 ±1.7	0.88	- 0.13± 1.6	0.71± 1.2	0.053
Resting HR (bpm)	0	64± 10	* 0.004	0	64 ±10	*0.007	-5.9 ±10.7	-18± 7.8	0.1
HR AT (bpm)	0	96 ±12	* 0.03	0	105 ±20	0.72	-6.7 ±21	-0.9± 16	0.27
Maximum HR (bpm)	0	117 ±21.4	0.21	0	127 ±21	0.86	-4 ± 22	1 ±10	0.15
Systolic RR at rest (mm HG)	0	124 ±16	0.14	0	139 ±19	0.09	-8 ±12	6 ±16	<b>*0.003</b>
Diastolic RR at rest (mm Hg)	0	72.6 ±9.5	* 0.03	0	83±7	0.32	-5 ±9	1.8 ±9	<b>*0.01</b>
VO2 AT (ml/min/kg)	0	16.6 ±12.7	0.11	0	17.4 ±8.1	0.09	2.5± 13.2	2.4 ±2.5	0.97
VO2 peak (ml/min/kg)	0	19.5 ±4.8	0.75	0	21.9 ±8.3	0.42	-0.4 ±2.7	1.76± 4.1	<b>*0.005</b>
O2/HR (ml/beat)	0	13.6 ±3.1	0.81	0	15.1 ±5.2	0.27	0.01± 3.1	1.6 ±3.3	0.08
dO2/HR (ml/min/W)	0	10.2 ±2.1	0.78	0	10.6 ±3.1	0.49	0.06 ±1.7	1.32± 3.5	0.18
VE/VCO2-slope	0	30.9 ±5.1	0.28	0	30.8 ±5.7	0.08	-1.56 ±5.3	-4.2 ±5	0.09
HRR (bpm)	0	55 ±20.6	0.29	0	64.3 ±24.8	0.06	3.5± 14.7	3.1 ±13.7	0.89
Lactate at 2 min (mmol)	1	1.5 ±0.9	0.17	2	1.3 ±0.35	0.051	-0.24 ±0.9	-0.32± 0.9	0.77
Lactate at 4 min (mmol)	1	1.9 ±1	0.07	2	1.7 ±0.67	*0.02	-0.2± 0.5	-0.46 ±1.1	0.39
Lactate at	1	2.6	* 0.02	2	2.3 ±0.8	*0.02	-0.4±	-0.97± 1.4	0.17

6 min (mmol)		±1.5				0.8			
Lactate at 8 min (mmol)	1	3.2 ±2.2	* 0.01	2	3.3 ±1.4	*0.03	- 0.98± 1.3	-0.5 ±0.38	0.15
Lactate at 10 min (mmol)	1	3.8 ±1.4	0.12	2	3.2 ±1.6	*0.03	-1.3 ±0.7	-0.96 ±0.5	0.23
EF (%)	2	55±9	* 0.001	0	60 ±10	0.18	-5±8	2±10	*0.004

#### Exercise Variables and EF

Table 3. Exercise characteristics of control group and interventional group at the end of the study period, mean ± SD, \*:p < 0.05 paired or unpaired t-test/Mann-Whiney U-Test

Variable	M V	End of Study Contr ol Grou p	P (versus Baselin e)	M V	End of study Interventio nal group	P (versus baselin e)	Delta Contr ol group	Delta Interventio nal group	P (delta control vs. delta interventio nal)
N=		42			19		42	19	
Total choleste rol (mmol/l)	3	149.2 ±33.7	0.96	1	151.8 ±40	0.48	3.3 ±26.5	-0.38± 27.4	0.64
LDL- choleste rol (mmol/l)	5	77.5 ±25.8	0.3	3	77.5 ±31.7	0.63	-10.5 ±64	-2.4± 26.2	0.57
HDL- choleste rol (mmol/l)	6	42.9 ±10.2	0.13	1	47.9 ±15.9	0.27	4.3 ±11	6.14 ±7.46	0.55
Fastenin g glucose (mg/dl)	8	98.6 ±44	0.1	4	104.7 ±22.3	0.38	-24 ±103	6 ±20.1	0.11
hsCRP (mg/dl)	2	1.67 ±1.4	0.19	7	2.3 ±5.1	0.32	-1.3± 2.8	-0.98 ±1.8	0.71
NT- proBNP (ng/l)	2	256.8 ±349	0.36	4	289.8± 408	0.31	- 153.5 ±382	-232 ±485	0.59
BMI (kg/m2)	0	28.2 ±3.2	0.65	0	27.3 ±4.5	0.17	-0.2± 0.7	-0.37 ±1.1	0.56

**Table 4: Blood parameters and BMI at the end of the study period, comparison between CG and IG, mean ± SD, p < 0.05 paired or unpaired t-test/Mann-Whiney U-Test**



Variable	M V	End of Study Contr ol Group	P (vers us Begin )	M V	End of study Interventio nal group	P (vers us begin )	Delta Contr ol group	Delta Interventio nal group	P (delta control vs. delta intervention al)
N=		42			19		42	19	
EQ-5D (Poinzt)	0	74.5 ±12.9	0.41	0	76.3 ±15	0.88	0.54± 10.7	0.64 ±13.9	0.98
HADS- Anxiety (Points)		19.2 ±3.2	0.8		19.3 ±1.9	0.51	-0.63 ±3.8	1.6 ±3.1	0.1
HADS- Depressi on (Points)		15.6± 1.8	0.37		15.6 ±1.1	0.64	0 ±1.6	1.36± 3.7	0.27

**Table 5: QoL-indices at the end of the study period, comparison between CG and IG**

All mean ± SD, p < 0.05 paired or unpaired t-test/Mann-Whiney U-Test, MV: missing value



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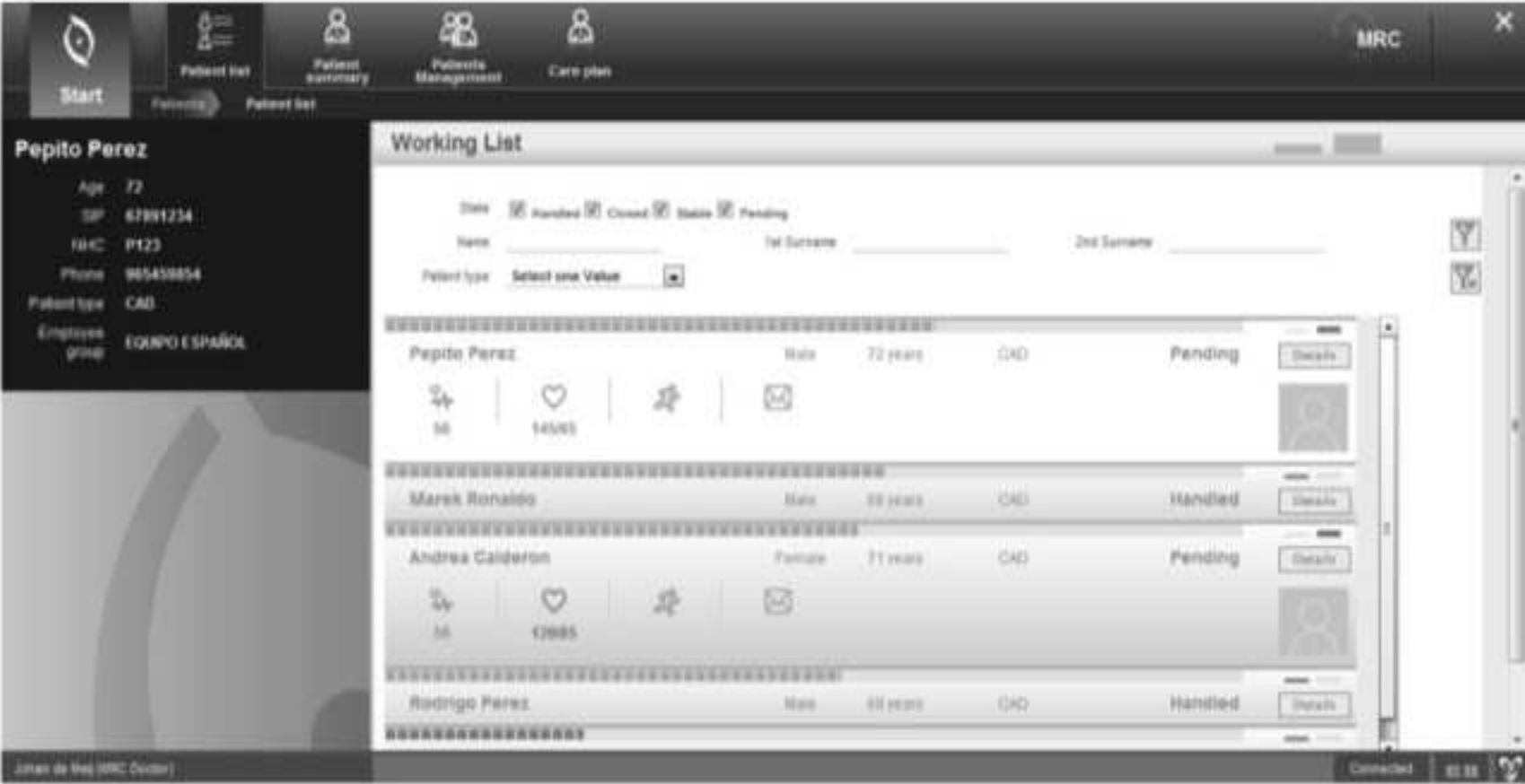


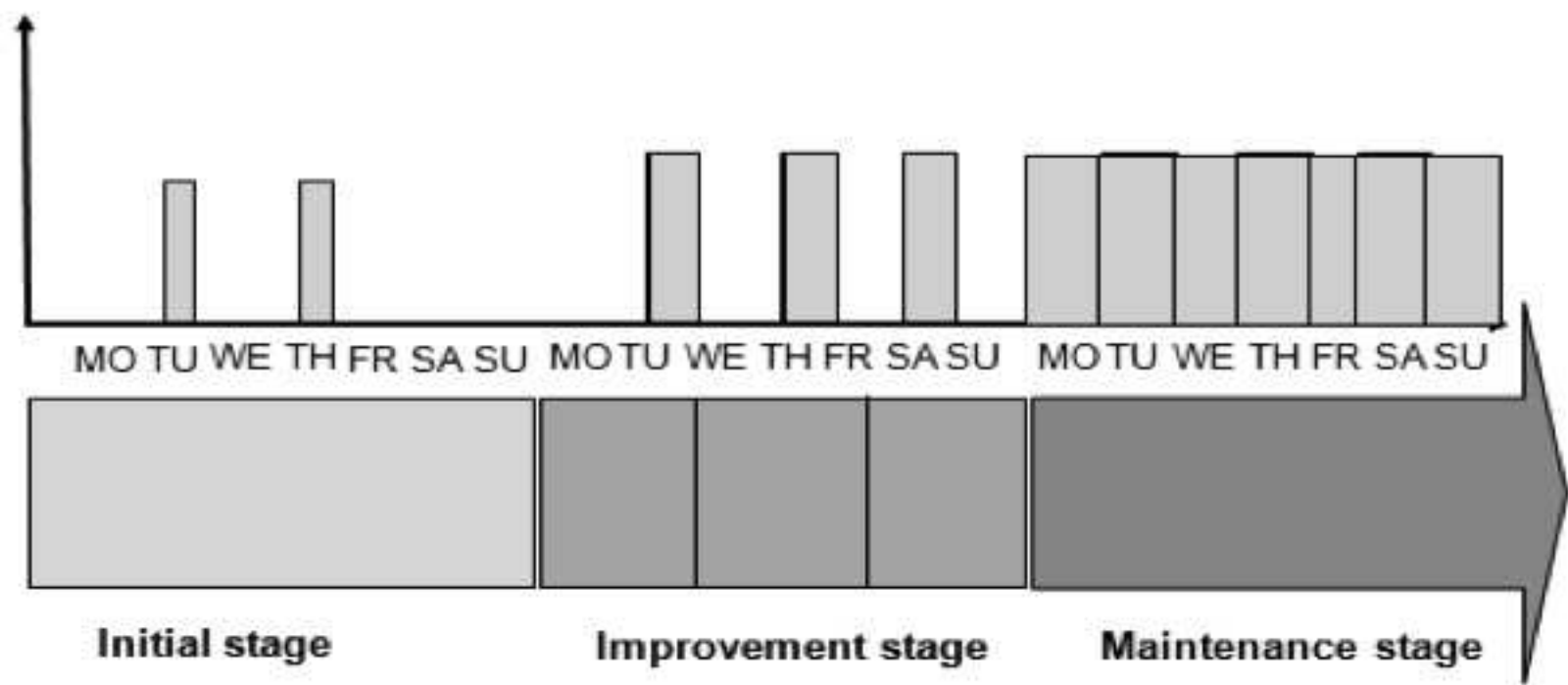
c)



d)

Figure 2





Phase	Length	Type / frequency	Duration	Intensity
Initial	3 weeks	Endurance 2x/w	3x10 – 30 min	11 @ Borg
Improvement – a	2 weeks	Endurance 2x/w Resistance 2x/w	3x10 – 30 min	12-13 @ Borg
Improvement – b	2 weeks	Endurance 2x/w Resistance 2x/w	3x15 – 45 min	12-13 @ Borg
Improvement – c	2 weeks	<b>Endurance 3x/w</b> <b>Resistance 3x/w</b>	3x15 – 45 min	12-13 @ Borg
Maintenance	12 + weeks	Endurance 3x/w-daily Resistance 3x/w	3x20 – 60 min	12-13 @ Borg